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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,425	03/03/2005	Tsuneko Okazaki	80161(302730)	9673

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EXAMINER	
HILL, KEVIN KAI	
ART UNIT	PAPER NUMBER
1633	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,425	OKAZAKI ET AL.	
	Examiner	Art Unit	
	KEVIN K. HILL	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,7,14,57 and 58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,7,14,57 and 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 3, 2010 has been entered.

Election/Restrictions

Applicant's response to the Requirement for Restriction, filed on October 1, 2007 is acknowledged.

Applicant has elected with traverse the invention of Group I, claim(s) 1, 3-7 and 13-14, drawn to a method of producing a circular mammalian artificial chromosome.

Within Group I, Applicant has elected the insertion sequence species "lox P site", as recited in Claim 13.

Amendments

Applicant's response and amendments, filed June 3, 2010, to the prior Office Action is acknowledged. Applicant has cancelled Claims 2-3, 5-6, 8-13 and 15-56, and amended Claim 1.

Claims 1, 4, 7, 14 and 57-58 are under consideration.

Priority

This application is a 371 of PCT/JP03/11134, filed September 1, 2003. Acknowledgment is made of Applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). Certified copies of the foreign patent applications Japan 2002-258114, filed September 3, 2002 and Japan 2002-338865, filed November 22, 2002 are filed with the instant application. Certified English translations of said foreign applications have not been provided.

Examiner's Note

Unless otherwise indicated, previous objections/rejections that have been rendered moot in view of the amendment will not be reiterated. The arguments in the June 3, 2010 response will be addressed to the extent that they apply to current rejection(s).

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

1. **The prior rejection of Claims 1, 4 and 57 under 35 U.S.C. 103(a)** as being unpatentable over Mejia et al (Genomics 70(2):165-170, 2000; *of record in IDS, AE), in view of Perkins et al (US 2003/0119104 A1), Waye et al (Mol. and Cell. Biol. 6(9):3156-3165, 1986) and Ikeno et al (Human Mol. Gen. 3(8):1245-1257, 1994; *of record in IDS, CE) **is withdrawn** in light of Applicant's amendment to the claims to recite the step of selecting a specific mammalian artificial chromosome having at least two copies of the first vector or two copies of the second vector or at least two copies of both the first and second vectors, a limitation that neither Mejia et al, Perkins et al, Waye et al nor Ikeno et al teach.

2. **The prior rejection of Claim 7 under 35 U.S.C. 103(a)** as being unpatentable over Mejia et al (Genomics 70(2):165-170, 2000; *of record in IDS, AE), in further view of Waye et al (Mol. and Cell. Biol. 6(9):3156-3165, 1986), Ikeno et al (Human Mol. Gen. 3(8):1245-1257, 1994; *of record in IDS, CE) and Perkins et al (US 2003/0119104 A1), as applied to claims 1, 4 and 57 above, and in further view of Bokkelen et al (U.S. Patent No. 5,695,967) **is withdrawn** for reasons discussed above.

3. **The prior rejection of Claim 14 under 35 U.S.C. 103(a)** as being unpatentable over Mejia et al (Genomics 70(2):165-170, 2000; *of record in IDS, AE), in further view of Waye et al (Mol. and Cell. Biol. 6(9):3156-3165, 1986), Ikeno et al (Human Mol. Gen. 3(8):1245-1257, 1994; *of record in IDS, CE), Perkins et al (US 2003/0119104 A1) and Bokkelen et al (U.S. Patent No. 5,695,967), as applied to claims 1, 4, 7 and 57 above, and in further view of Cooke et al (WO 00/18941) **is withdrawn** for reasons discussed above.

4. **The prior rejection of Claim 58 under 35 U.S.C. 103(a)** as being unpatentable over Mejia et al (Genomics 70(2):165-170, 2000; *of record in IDS, AE), in further view of Waye et al (Mol. and Cell. Biol. 6(9):3156-3165, 1986), Ikeno et al (Human Mol. Gen. 3(8):1245-1257, 1994; *of record in IDS, CE), Perkins et al (US 2003/0119104 A1), Bokkelen et al (U.S. Patent No. 5,695,967) and Cooke et al (WO 00/18941), as applied to claims 1, 4, 7, 14 and 57 above, and in further view of Okazaki et al (WO 98/08964) **is withdrawn** for reasons discussed above.

5. **Claims 1, 4 and 57 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Mejia et al (Genomics 70(2):165-170, 2000; *of record in IDS, AE), in view of Perkins et al (US 2003/0119104 A1), Waye et al (Mol. and Cell. Biol. 6(9):3156-3165, 1986), Ikeno et al (Human Mol. Gen. 3(8):1245-1257, 1994; *of record in IDS, CE), Ikeno et al (Nature Biotech. 16:431-439, 1998; of record in IDS) and Bigger et al (J. Biol. Chem. 276(25):23018-23027, 2001).

Determining the scope and contents of the prior art.

The teachings of Mejia et al, Perkins et al, Waye et al and Ikeno et al (1994) are discussed in prior Office Actions, and incorporated herein.

Mejia et al teach that the Cre-mediated method may be used to integrate at least two genomic inserts into a first vector (pg 169, col. 1, last ¶).

Ikeno et al (1998) taught the step of selecting from selected transformed cells a cell containing a specific mammalian artificial chromosome having at least two copies of the first vector and/or at least two copies of the second vector (pg 435; pg 436, Table 3). Ikeno et al taught that a vector comprising a mammalian centromere sequence comprising an 11-mer repeat obtained from human chromosome 21 can naturally multimerize by recombination or amplification when producing an MAC in a eukaryotic host cell via homologous recombination (pg 437, col. 2).

Similarly, Bigger et al taught that the formation of high-molecular multimers by homologous recombination between circular molecules naturally flows from the activity of Cre recombinase (Figure 5).

Considering objective evidence present in the application indicating obviousness or nonobviousness.

The focus when making a determination of obviousness should be on what a person of ordinary skill in the pertinent art would have known at the time of the invention, and on what such a person would have reasonably expected to have been able to do in view of that knowledge. This is so regardless of whether the source of that knowledge and ability was documentary prior art, general knowledge in the art, or common sense. M.P.E.P. §2141.

It would have been obvious to one of ordinary skill in the art to select from selected transformed cells a cell containing a specific mammalian artificial chromosome having at least

two copies of the first vector comprising a mammalian centromere sequence comprising an 11-mer repeat unit and/or at least two copies of the second vector comprising an insulator sequence and an insertion sequence, i.e. a loxP site, in a method of producing a mammalian artificial chromosome because high-molecular multimers comprising the first and/or second vector were recognized in the prior art to be naturally occurring products from homologous recombination reactions [Ikeno et al, 1998; Bigger et al]. An artisan would be motivated to select from selected transformed cells a cell containing a specific mammalian artificial chromosome having at least two copies of the first vector comprising a mammalian centromere sequence comprising an 11-mer repeat unit and/or at least two copies of the second vector comprising an insulator sequence and an insertion sequence, i.e. a loxP site, in a method of producing a mammalian artificial chromosome because Ikeno et al (1994) taught that human chromosome 21 alphoid arrays [repeat units of about 1.5kb comprising the 11-mer] naturally exist in higher order structures in mammalian chromosomes, i.e. 1.3Mb (500Kb+480Kb+20Kb+330Kb) (Figure 4). Furthermore, Ikeno et al (1998) taught that the larger minichromosomes comprising at least two copies of the first vector and/or at least two copies of the second vector appear to be more stable, achieving a segregation efficiency of 99.5% (pg 434). Artificial chromosomes which lack centromeric activity are rapidly lost in mammalian cells; whereas, higher order alphoid repeats are capable of conferring autonomous replication onto a recombinant nucleic acid in mammalian cells (pg 437, col. 1; pg 438, col. 1).

Thus, it would be common sense for the ordinary artisan to select for multiple [at least two] copies of a vector comprising a mammalian centromere sequence comprising an alphoid 11-mer repeat obtained from human chromosome 21 as such would reflect normal high-molecular multimer present in normal centromeres and providing normal centromere function, and the ordinary artisan could reasonably predict that by increasing the copy number of the mammalian centromere sequence comprising an 11-mer repeat obtained from human chromosome 21, one could improve the retention of the artificial chromosome in the host cell through subsequent generations.

The cited prior art meets the criteria set forth in both *Graham* and *KSR*, and the teachings of the cited prior art provide the requisite teachings and motivations with a clear, reasonable

expectation of success. Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

6. **Claim 7 is rejected under 35 U.S.C. 103(a)** as being unpatentable over Mejia et al (Genomics 70(2):165-170, 2000; *of record in IDS, AE), in further view of Waye et al (Mol. and Cell. Biol. 6(9):3156-3165, 1986), Ikeno et al (Human Mol. Gen. 3(8):1245-1257, 1994; *of record in IDS, CE), Perkins et al (US 2003/0119104 A1), Ikeno et al (Nature Biotech. 16:431-439, 1998; of record in IDS) and Bigger et al (J. Biol. Chem. 276(25):23018-23027, 2001), as applied to claims 1, 4 and 57 above, and in further view of Bokkelen et al (U.S. Patent No. 5,695,967).

7. **Claim 14 is rejected under 35 U.S.C. 103(a)** as being unpatentable over Mejia et al (Genomics 70(2):165-170, 2000; *of record in IDS, AE), in further view of Waye et al (Mol. and Cell. Biol. 6(9):3156-3165, 1986), Ikeno et al (Human Mol. Gen. 3(8):1245-1257, 1994; *of record in IDS, CE), Perkins et al (US 2003/0119104 A1) Ikeno et al (Nature Biotech. 16:431-439, 1998; of record in IDS), Bigger et al (J. Biol. Chem. 276(25):23018-23027, 2001) and Bokkelen et al (U.S. Patent No. 5,695,967), as applied to claims 1, 4, 7 and 57 above, and in further view of Cooke et al (WO 00/18941).

8. **Claim 58 is rejected under 35 U.S.C. 103(a)** as being unpatentable over Mejia et al (Genomics 70(2):165-170, 2000; *of record in IDS, AE), in further view of Waye et al (Mol. and Cell. Biol. 6(9):3156-3165, 1986), Ikeno et al (Human Mol. Gen. 3(8):1245-1257, 1994; *of record in IDS, CE), Perkins et al (US 2003/0119104 A1) Ikeno et al (Nature Biotech. 16:431-439, 1998; of record in IDS), Bigger et al (J. Biol. Chem. 276(25):23018-23027, 2001), Bokkelen et al (U.S. Patent No. 5,695,967) and Cooke et al (WO 00/18941), as applied to claims 1, 4, 7, 14 and 57 above, and in further view of Okazaki et al (WO 98/08964).

Response to Arguments

Applicant argues that no combination of Mejia with any of the secondary references cited expressly or inherently teaches the invention as claimed. None of the Waye et al., Ikeno et al., Perkins et.

al. Bokkelen or Cooke et al or Okazaki et al references cures the defects of the Mejia reference and teaches a mammalian centromere sequence as claimed.

Applicant's arguments have been fully considered, but are unpersuasive. The Examiner's response to Applicant's argument regarding the instantly claimed invention is discussed above and incorporated herein.

Applicant is respectfully reminded that at the time of the invention, α satellite (alphoid) DNA was known in the prior art to form a functional centromere in a human artificial chromosome, wherein the presence of a centromere protein B sequence (CENP-B box) in the alphoid DNA is a requirement for the functional centromere. Waye et al taught the sequence of the human chromosome 17 centromere comprising nucleic acid sequences 100% identical to SEQ ID NO:1. Furthermore, Ikeno et al taught a consensus CENP-B box nucleotide sequence from human chromosome 21 alphoid repeats, wherein the human chromosome 17 centromere comprises an 11-mer repeat with 100% identity to the consensus sequence set forth by Ikeno et al.

Absent evidence to the contrary, nothing non-obvious is seen with substituting a mammalian centromere sequence comprising an 11mer repeat unit obtained from human chromosome 17 with a mammalian centromere sequence comprising an 11mer repeat unit obtained from human chromosome 21 because both such centromere sequences comprise an 11-mer repeat with 100% identity to the consensus sequence set forth by Ikeno et al of the consensus CENP-B box nucleotide sequence, and thus are considered functional equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). See MPEP §2144.06

Similarly, it would have been obvious to one of ordinary skill in the art to substitute a mammalian centromere sequence comprising an 11mer repeat unit obtained from human chromosome 17 with a mammalian centromere sequence comprising an 11mer repeat unit obtained from human chromosome 21 comprising SEQ ID NO:3 with a reasonable expectation of success because the simple substitution of one known element for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. M.P.E.P. §2144.07 states "The selection of a known material based on its suitability for its intended use supported a *prima facie* obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)". When substituting equivalents known in the prior art for the same purpose, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). M.P.E.P. §2144.06. An artisan would be motivated to substitute a mammalian centromere sequence comprising an 11mer repeat unit obtained from human chromosome 17 with a mammalian centromere sequence comprising an 11mer repeat unit obtained from human chromosome 21 comprising SEQ ID NO:3 because Applicant's own prior work successfully demonstrated a method of producing a mammalian artificial chromosome comprising a centromere obtained from human chromosome 21 comprising SEQ ID NO:3 and teach that the nucleic acid has sufficient quantity of CENP-B box spaced repeats to provide centromere properties to a DNA construct in a host cell.

The cited prior art meets the criteria set forth in both *Graham* and *KSR*, and the teachings of the cited prior art provide the requisite teachings and motivations with a clear, reasonable expectation of success. Thus, absent evidence to the contrary, the invention as a whole is *prima facie* obvious.

Conclusion

9. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Kevin K. Hill whose telephone number is 571-272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kevin K. Hill/
Primary Examiner, Art Unit 1633